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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/622,068	LEGARDA IBANEZ, JUAN JOSE	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/16/05;9/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The Information Disclosure Statements filed May 16, 2005 and September 9, 2005 have been reviewed and considered, see the enclosed copy of PTO FORM 1449. However, with regard to reference citation Nos. 15, 21 and 27, only the abstracts were provided rather than the whole documentation as indicated by the Applicants. Accordingly, the correction was made on the PTO Form 1449 to reflect only the abstracts were cited by the Examiner.

Specification

The disclosure is objected to because of the following informalities: It appears the insertion of "[sic? flupenthixol]" is in result of an error, on page 2, line 16.

Appropriate correction is required.

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims

are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 23-37 been renumbered as 21-35, respectively.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19-35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 14, 16, 17, 19, 20-27 and 29 of copending Application No. 11/111,435 in view of Hadcock et al. (U.S.Patent No. 6,451,783B1). The instant application and copending application are directed to overlapping subject matter wherein both applications are directed to treatment of stimulant abuse employing same active agent (flumazenil). The instant

claims are obviated and encompassed by copending Application because Hadcock et al. teach on column 11, lines 29-32, that cocaine is a stimulant. It would have been obvious to one of ordinary skill in the art to utilize flumazenil for the treatment of specific stimulant abuse such as cocaine since cocaine is well-know stimulant by Hadcock et al. The dosing intervals and divided daily effective amounts of instant claims are obvious modification since they are within the knowledge of one of ordinary skill in the art. One of ordinary skill in the art would optimize the dosing intervals and to divided daily dosage of treating cocaine dependency according to patient's conditions, severity and the factors concerning concurrent medical regimen.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 32 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "reducing desire to use cocaine", does not reasonably provide enablement for "**eliminating** desire to use cocaine". The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to practice the invention commensurate in scope with these claims.

3. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a method for treating cocaine dependency, comprising administering a therapeutically effective amount of flumazenil to a patient in need of such treatment wherein the flumazenil reduces or **eliminates** the desire to use cocaine. The nature of the invention is extremely complex in that it encompasses the **actual elimination** of desire to use cocaine (e.g. cocaine craving) such that the subject treated with above compound **totally eliminates** desire to use cocaine.

Breath of the Claims: The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass actual **elimination** of a complex cocaine desire in cocaine dependency in patients which involves potentially many different biological psychological experiences (i.e. psychic dependence, psychic addiction, euphoric excitement and

hallucinatory). Each of which may or may not be addressed by the administration of the claimed compound.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compound to a patient in order **to actually eliminate** cocaine desire is minimal. All of the guidance provided by the specification is directed towards reduction of desire rather than **total elimination** of desire of cocaine.

Working Examples: All of the working examples provided by the specification are directed toward **the reduction rather than elimination** of cocaine desire.

State of the Art: While the state of the art is relatively high with regard to reduction of cocaine desire in cocaine dependency (e.g. cocaine craving), the state of the art with regard to **elimination** of such condition is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to **eliminate** development of cocaine desire. The state of art (Halikas U.S.Patent No. 5,028,611, column 1, lines 1-20) report that the treatment of cocaine abuse has been **largely ineffective**, based on cocaine relapse rates and that depending on the level of habituation or dependence and prognostic features the cocaine dependent patients relapse within the first 12 months no matter how high their motivation and this relapse rate is due to an **overwhelming "craving"** for cocaine. The state of art (DeVincent U.S.Patent No. 5,229,120, column, 1, lines 46-60) reports that at present, no uniformly effective pharmacotherapy for

cocaine dependence and the attempts to treat users of cocaine by administering a less harmful or less pleasurable drug in its place have yielded **inconsistent results**. Further, the treatment programs can result in a substitute addiction and **may even stimulate relapse to cocaine abuse**.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the **total elimination** of cocaine desire in a patient with the claimed compound makes practicing the claimed invention unpredictable in terms of **elimination** of cocaine desire.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, **duration** of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for **absolute elimination** of cocaine desire. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard to elimination of cocaine desire with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding **elimination of cocaine**

desire with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to eliminate the development of cocaine desire by administration of one of the claimed compound in cocaine dependent patient.

Therefore, a method for treating cocaine dependency comprising administering a therapeutically effective amount of flumazenil wherein flumazenil is administered to reduce or **eliminates** the desire to use cocaine is not considered to be enabled by the instant specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "**short**" and "**small**" in claim 20 are relative terms which renders the claim indefinite. The terms "**short**" and "**small**" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the

invention. The terms are indefinite since the "**short**' time interval and "**small**" quantities vary among the one of ordinary skill in the art.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19, 26, 28 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Uki et al. (Jpn. J. Alcohol & Drug Dependence, 1994) of record.

Uki et al. teach **flumazenil** was administered **intraperitoneally (parenteral)** in **cocaine intoxicated** rats for its preventive effect on seizure. Flumazenil at a dose 0.125mg/kg extended the onset time of the cocaine induced seizure and Flumazenil at 0.5 or 1mg/kg with **diazepam (an additional agent)** 2mg/kg prevented the seizure and kept righting reflex. (summary).

This teaching is anticipatory since instant specification on page 4 lines 4-6, recites "cocaine dependency" includes "cocaine abuse" and that cocaine intoxicated rats taught by Uki et al. are abused with cocaine as the rats were intoxicated with cocaine. Accordingly, the effect of reducing or eliminating the desire to use cocaine would be inherent upon the same method steps of Uki et al. for the same purpose as

instantly claimed for treating cocaine dependency comprising the administration of same active agent administered to same patient (cocaine intoxicated or cocaine abused rats) with same therapeutically effective amount.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20-25, 27, 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uki of record as applied to claims 19, 26, 28 and 32 above, and further in view of Derlet et al. (Neuropharmacology, 1990) of record.

Uki et al's teaching as applied as before.

Uki et al. do not expressly teach the short time intervals in small quantities set forth in claim 20, specific quantities and/or dosing intervals forth in claims 21-25, 33 and 34 and the intravenous route of administration set forth in claim 27.

Derlet et al. teach **rats** tested for experiments involving cocaine-induced toxicity pretreated with flumazenil are **Male Sprague-Dawley rat, weighing between 200 and 300g.**

It would have been obvious to one of ordinary skill in the art that Uki et al's rats administered with amounts **0.5 or 1mg/kg** flumazenil encompasses Applicant's dosing

quantities between about 0.1 and about 0.3mg set forth in claim 22 because the rats routinely tested for experiment involving cocaine-induced toxicity weigh between 200 and 300g as taught by Derlet et al. and the amounts employed by Uki as 0.5mg/kg would equal to 0.1mg for 200g rats and 1mg/kg administered to 300g rats would equal to the amount of 0.3mg. Moreover, the dose given 0.5mg or 1mg administered kg per rats by Uki et al. obviates the "small quantities" set forth in Applicant's claim 20 because is the amounts expressed in decimals under one would be considered very "small" number. With regard to amount of daily dosage set forth in Applicant's claims 24 and 34, the route of administration set forth in claim 27 and the dosing intervals set forth in claims 20, 21, 25 and 33 are all deemed obvious since as anyone of ordinary skill in the art will appreciate, preferred dosages and the route of administration such as intraperitoneal injection are merely exemplary and serve as useful guideposts for the physician or one of ordinary skill in the art. There are, however, many reasons for varying daily dosages and route of administration including by orders of magnitude; for instance, an extremely heavy patient or one having an unusually severe condition would require correspondingly higher dosage and the patients with sensitive gastrointestinal system would require the administration of given dosage in a short time intervals with small quantities at a time. Further, route of administration would vary, for example, intravenous route of administration is preferred when the subject has oral injury or surgery and unable to use the oral routes. One would be motivated to optimize the specific quantities and/or dosing intervals and the route of administration according to a physiology, severity of condition and medical history of patients being treated.

Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uki of record as applied to claims 19, 26, 28 and 32 above, and further in view of Gasior et al. (The Journal of Pharmacology and Experimental Therapeutics, 2000).

Uki et al's teaching as applied as before.

Uki et al. do not teach the treatment with clomethiazole set forth in claim 29.

Gasior et al. teach that chlormethiazole (also known as clomethiazole) is effective against toxic effects such as seizure caused by cocaine. (title, abstract, page 154, fig. 1).

It would have been obvious to one of ordinary skill in the art to employ chlormethiazole in Uki's experiment for the treatment of cocaine dependency because clomethiazole is effective of treating the symptoms related to cocaine dependency such as seizure as taught by Gasior et al. One would have been motivated to incorporate clomethiazole in Uki's experiment for the treatment of symptoms related to cocaine intoxication (abuse) in order to achieve at least an additive effect in treatment of symptoms such as seizure caused by cocaine dependency (abuse). The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)) for effectiveness in treatment of cocaine induced seizures.

Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uki et al. of record as applied to claims 19, 26, 28 and 32 above, and further in view of Yelle (U.S.Patent No. 6,468,997B2).

Uki et al. as applied as before.

Uki et al. do not teach the additional agent such as fluoxetine set forth in claim 32.

Yelle teaches treatment of substance abuse including cocaine abuse comprising a composition comprising employment of fluoxetine as an additional agent. (abstract, column 4, lines 19-24, column 3, lines 19-30).

It would have been obvious to one of ordinary skill in the art to incorporate fluoxetine as a additional agent in flumazenil regimen taught by Uki et al. because fluoxetine is routinely employed as a additional agent for the regimen involving treatment of cocaine abuse as taught by Yelle et al. One would have been motivated to employ fluoxetine to Uki et al's cocaine abuse treatment in order to achieve a routine cocaine abuse treatment well known to incorporate fluoxetine as an additional agent. Absent any evidence to contrary, there would have been a reasonable expectation of successfully treating cocaine dependency including cocaine abuse by incorporating fluoxetine with flumazenil both well-known in regimen involving cocaine abuse treatment.

Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uki of record as applied to claims 19, 26, 28 and 32 above, and further in view of Woolf (Cocaine Poisoning, Clinical Toxicology Review, 1995) of record.

Uki et al. as applied as before.

Uki et al. do not teach the administration of flumazenil under sedation set forth in claim 31.

Woolf teaches that cocaine poisoning treatment may require a patient to be under sedation for agitation due to the toxicity. (page 4, under treatment first paragraph).

It would have been obvious to one of ordinary skill in the art to administer flumazenil to Uki's rats under sedation because sedation may needed in the patients (rats) being treated when the agitation occurs as taught by Woolf. One would have been motivated to administered flumazenil under sedation in order to successfully manage and prevent agitation due to cocaine toxicity. Absent any evidence to contrary, there would have been a reasonable expectation of successfully treating cocaine abuse with flumazenil while the patient is under sedation in order to control and prevent agitation.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 5:30 am to 2 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jennifer Kim
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April 12, 2006